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Pathophysiology of Placenta Accreta Spectrum Disorders: A Review of Current Findings

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Abstract:	Current findings continue to support the concept of a biologically defective decidua rather than a primarily abnormally invasive trophoblast. Prior caesarean sections increase the risk of placenta praevia and both adherent and invasive placenta accreta, suggesting that the endometrial/decidual defect following the iatrogenic creation of a uterine myometrium scar has an adverse effect on early implantation. Preferential attachment of the blastocyst to scar tissue facilitates abnormally deep invasion of trophoblastic cells and interactions with the radial and arcuate arteries. Subsequent high velocity maternal arterial inflow into the placenta creates large lacunae, destroying the normal cotyledonary arrangement of the villi.

Pathophysiology of Placenta Accreta Spectrum Disorders: A Review of Current Findings

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Conflict of interest

The authors have no conflicts of interest to declare.

Abstract

Current findings continue to support the concept of a biologically defective decidua rather than a primarily abnormally invasive trophoblast. Prior caesarean sections increase the risk of placenta praevia and both adherent and invasive placenta accreta, suggesting that the endometrial/decidual defect following the iatrogenic creation of a uterine myometrium scar has an adverse effect on early implantation. Preferential attachment of the blastocyst to scar tissue facilitates abnormally deep invasion of trophoblastic cells and interactions with the radial and arcuate arteries. Subsequent high velocity maternal arterial inflow into the placenta creates large lacunae, destroying the normal cotyledonary arrangement of the villi.

Key Words: Placenta accreta; placenta increta; placenta percreta; ultrasound diagnosis; histopathology.

Definitions

- Placenta accreta: general term used to describe the different levels or grades of the accrete placenta spectrum.
- Placenta creta: histologic description of placental villi adherent to the myometrium without interposing decidua.
- Placenta increta: clinical description of placenta villi invading the myometrium down to the uterine serosa.
- Placenta percreta: clinical description of placenta villi invading the entire uterine wall and beyond.
- Morbidly adherent placenta: 19th Century clinical terminology used to describe placenta retention due to various causes including placenta creta.

Introduction

To understand the pathophysiology of accreta placentation it is essential to look into the history of its epidemiology. The first case reports of placenta accreta (PA) were published in the literature in the 1920s, and the first series in 1937 by the obstetrician Frederick C. Irving and the pathologist Arthur T. Hertig from the Boston Lying-In Hospital [1]. In 1927, Dr DS Forster, a scholar in gynaecology at the Pathology Department of the Montreal General Hospital, Montreal, Canada described a case of PA with invasive villi following a prior caesarean delivery (CD) [2]. This was the only case in 8,000 deliveries during a 6-year period at the Montreal maternity hospital, indicating the rarity of the condition at that time. Modern caesarean sections were introduced in obstetric practice at the end of the 19th century, but were seldom performed until the 1920s [3]. Not surprisingly, only one of the 20 cases of PA personally treated by Irving and Hertig occurred after a previous CD [1]. Similarly, in their review of 86 case reports up to 1935, only one was found after a prior CD. They concluded that the predisposing factors of PA at the time were a previous manual delivery and/or “vigorous” uterine curettage. They calculated the prevalence of accreta placentation in their population to be around 1 in 1,956 deliveries. The paper by Irving and Hertig was published in a journal that no longer exists and thus is not recorded in PubMed. There are no other publications on placenta accreta between 1927 and 1944.

Major technical advances in surgical and anaesthetic techniques and the advent of antibiotics and blood transfusions in the 1940s substantially reduced the morbidity and mortality of CD [3]. As a consequence, increasingly women not only survive the procedure but also are able to have one or more subsequent pregnancies. Before the

advent of ultrasound and magnetic resonance imaging (MRI), the diagnosis of PA was exclusively clinical and made at birth. In the 1920s, PA was diagnosed “when the placenta fails to be delivered, following the birth of the child” [2]. Irving and Hertig defined PA as the abnormal adherence either in whole or in part of “the afterbirth” to the underlying uterine wall [1]. Their study became a “classic” but none of their cases had villous tissue invading the myometrium. This fact has led to a lot of confusion for obstetricians struggling with the delivery of a “sticky” placenta. Indeed, the clinical definition of a superficially adherent PA is very similar to that of placental retention and has not changed since the 1930s.

Like for all other life-threatening pathologies in obstetrics and gynaecology, histopathologic examination remains the gold diagnostic standard to evaluate epidemiologic trends and calculate health care provision. It is essential to confirm the depth of villous invasion of the uterine myometrium in order to improve clinical management. Histopathologic examination also permits immunohistochemical (IHC) and molecular biological studies of the underlying mechanisms leading to abnormal adherence or invasive placentation. We present here a review the recent findings on the pathophysiology of PA. To facilitate the discussion, we use the term placenta accreta spectrum (PAS) to include both adherent and invasive placental disorders.

BACKGROUND EPIDEMIOLOGY

By 1966, when Luke et al, published their series of PAS, nine of their 21 cases had a previous history of CD [4]. All recent epidemiologic studies have shown a clear association between the CD rate and the incidence of accreta placentation in

subsequent pregnancies [5-8]. There has been an exponential increase in global rates of CD, which was particularly marked over the past 25 years with rates increasing from less than 7% in 1990 to over 19% in 2014 [9]. Currently, the highest regional CD rates are found in Latin America (40-50%) and the lowest in sub-Saharan Africa (3-6%). In Europe, the CD rates vary from 22% in the North to 31% in the South, whereas in Northern America the CD rate is now 32.3%. Countries such as Egypt, Turkey, Brazil have national CD rates over 55% and rising [10]. The incidence of PAS increases with the number of prior CDs [5-8], and a previous caesarean section has been the main cause of PAS for the last two decades [8]. Changes in the prevalence of PAS secondary to changes in CD rates are often delayed by one or two decades [8] depending on local birth rates. Thus, countries with both a high birth rate and a very high CD rate and rising, such as Egypt, will soon have the highest maternal morbidity and mortality due to PAS.

For an unknown reason, placenta accreta including its invasive forms increta and percreta, has increasingly been referred to as “morbidly adherent” placenta or MAP which is a 19th century terminology used to describe placental retention after delivery. Many modern authors still use the old clinical criteria to define an accreta placenta i.e. difficult manual, piecemeal removal of the placenta, absence of spontaneous placental separation 20-30 min after birth despite active management including bimanual massage of the uterus, use of oxytocin and controlled traction of the umbilical cord, retained placental fragment requiring curettage after vaginal birth and heavy bleeding from the placentation site after removal of the placenta during CD [11,12].

Since the 1920s, the primary method of management has been emergency

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4 hysterectomy, with the diagnosis being confirmed by histopathologic examination in
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6 most case reports and series. Although the vast majority of PAS cases diagnosed
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8 prenatally or at delivery are still managed by hysterectomy, more than half of the
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10 authors do not provide detailed data on histopathologic confirmation of the diagnosis of
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12 placenta accreta and even more very rarely on the differential diagnosis between
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14 adherent and invasive accreta [13,14]. Thus, many cohort studies on the diagnosis and
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16 management of PAS include a mixed bag of cases with various degrees of invasion of
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18 the myometrium by chorionic villi. The MAP terminology excludes the more invasive
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20 forms of accreta placentation, and adds to the confusion in the clinical differential
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22 diagnosis at delivery between PAS and placental retention [14]. This lack of precise
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24 diagnosis can explain the wide variation in incidence and prevalence of PAS reported in
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26 the international literature in the last two decades [8].
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34 The single other most important risk factor, reported in around 50% of all cases
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36 of PAS disorders, is placenta previa. The risk of previa also increases with the number
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38 of prior CDs [8]. Women with a prior history of CD, presenting with a low-lying placenta
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40 or placenta previa, now represent the group with the highest risk of PAS [13]. This
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42 epidemiologic association also indicates that a previous uterine scar can have an
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44 impact on both implantation and placentation.
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51 **ACCRETA PLACENTATION**

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55 Irving and Hertig were the first to suggest that the pathological basis of PAS is the
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57 complete or partial absence of the decidua basalis [1]. Since then, several concepts
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59 have been proposed to explain why and how PA occurs [10,15]. The oldest concept is
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4 based on a theoretical primary defect of trophoblast biology leading to excessive
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6 attachment or invasion of the myometrium. The current hypothesis is that of a
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8 secondary defect of the endometrial-myometrial interface leading to a failure of normal
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10 decidualisation in the area of the uterine scar allowing abnormally deep placentation. An
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12 abnormal vascularisation resulting from the scaring process after surgery, with
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14 secondary localized hypoxia leading to both defective decidualization and excessive
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16 trophoblastic invasion, has also been suggested [16].
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24 ***Development of the uterine scar***

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27 Major surgical procedures such as caesarean sections or myomectomies that cut
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29 through the entire uterine wall will leave a scar through all the smooth muscular layers
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31 of the myometrium. Unlike the epithelial layers of the endometrium and uterine
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33 peritoneum that heal by regeneration and recolonization of scar area, the myometrium,
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35 does not heal by regenerating muscle fibers, but by forming “foreign” substances
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37 including collagen [15]. Myofibre disarray, tissue edema, inflammation and elastosis
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39 have all been observed in uterine wound healing after surgery. The resulting scar tissue
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41 is less elastic and more prone to injury/rupture in subsequent pregnancies than the
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43 intact muscle. Different surgical techniques such as single-layer versus double-layer
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45 closure of the myometrium, locked versus unlocked single-layer closure [8] or the suture
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47 material used for the closure may have an influence on the healing process and the
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49 risks of uterine rupture, but the evidence regarding the risk of PAS in subsequent
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51 pregnancies remains limited.
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59 Compared with women with a primary CD, women who undergo a repeat
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cesarean are more than twice as likely to have PAS disorders [8]. Multiple CD (MCD) scars are often associated with a clear loss of myometrium or a defect (Fig. 1A) with a direct communication between the endometrial cavity and the visceral serosa [15]. Residual myometrial thickness is greater and scar defect length, but not depth and width, is shorter following double-layer compared with single-layer closure. Large caesarean scar defects (CSD) may lead to scar dehiscence with advancing gestation (Fig 1.B), and could even explain rare reports of placenta percreta leading to uterine rupture in the first half of pregnancy. Although this is an extremely rare complication of placentation, the mechanism of uterine rupture due to a placenta percreta is likely to be similar to that of a tubal rupture in an ectopic placentation. The strong epidemiologic association between placenta previa and PAS findings suggest that the decidual defect following the artificial creation of a scar in the uterine myometrium has an adverse effect on both early implantation by creating conditions for preferential attachment of the blastocyst to scar tissue and facilitating abnormally deep placental invasion.

Leukocyte recruitment to the endometrium is observed during the normal secretory phase, and has been reported to be increased following a CD [10,15]. A prior CD increases not only the risk of PAS in subsequent pregnancies but also the risk of placenta praevia [8], suggesting a tropism of the blastocyst for the scar area. The uterine artery resistance is increased, and the volume of uterine blood flow as a fraction of maternal cardiac output is decreased in women with a previous CD compared to women with a previous vaginal birth [17]. Overall, these data suggest a possible relationship between a poorly vascularized uterine scar area and an increase in the resistance to blood flow in the uterine circulation. A large scar area resulting from MCD

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4 and scar dehiscence is likely to have an impact on endometrial re-epithelialisation.
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6 Decidualization may be sparse or absent in the overlying area and the absence of
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8 structured myometrium underneath is more likely to lead to invasive (increta or percreta)
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10 PAS.
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14 PAS is not exclusively a consequence of caesarean scar and any form of
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16 damage, even small, to the integrity of the uterine lining following curettage,
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18 myomectomy, or endometrial resection has been associated with PAS in subsequent
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20 pregnancies [8,10]. Uterine anomalies, adenomyosis and submucous fibroids have also
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22 been associated with PAS in primigest women [8]. Endometritis can lead to endometrial
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24 fibrosis and poor decidualization and thus to development of PAS. This can explain why
25
26 before the advent of antibiotics a prior manual removal of the placenta with or without a
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28 uterine curettage was the main factor associated with PAS in subsequent pregnancies
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30 [1]. The trauma to the myometrium and the surface of the endometrium is often limited
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32 in a curettage procedure, and should not be associated with the absence of re-
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34 epithelialization of the scar area and changes in the surrounding uterine circulation
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36 compared with the larger and deeper scars resulting from MCD. If the myometrium scar
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38 is small, the placenta may simply grow over it, which can explain why more than 90% of
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40 cases of placenta praevia in women with one prior CD are not accreta [10]. Within this
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42 context, if PAS develops it is more likely to be superficial (adherent) and focal.
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54 ***Characteristics of the accreta trophoblast***

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57 There are two types of trophoblast: the villous trophoblast which covers the placental
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59 villi and which is made up of cytotrophoblast cells and the syncytiotrophoblast, and the
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extravillous trophoblast (EVT) which arises from the distal tips of the anchoring villi that normally make contact with the decidua basalis. The EVT differentiate primarily into interstitial and endovascular cells sub-populations that migrate through the decidual stroma and down the lumens of the spiral arteries respectively. The interstitial EVT invade the uterine wall as far as the inner third of the uterine myometrium, also called the junctional-zone (JZ), where they fuse to form multinucleated trophoblast giant cells (MNGCs) [10,18]. In the weeks following implantation, EVT cells are found both within and around the spiral arteries in the central area of the placenta. EVT gradually migrate laterally, reaching the periphery of the placenta around mid-gestation. Endovascular EVT cells in the central area, destined to become the definitive placenta, act as plugs blocking the spiral arteries. These plugs prevent a continuous flow of maternal blood from entering the placenta during most of the first trimester [18]. This phenomenon creates an environment of physiological hypoxia inside the gestational sac, which is essential for normal fetal-placental development and which modulates the formation of the membranes of definitive placenta.

Both endovascular and interstitial EVT invasion are associated with the physiological conversion of the terminal part of the uterine circulation, extending as far the basal part of the spiral arteries at the level of the JZ or the inner third of the myometrium [10]. Around 30-50 spiral arteries are transformed during the first trimester. In normal pregnancies, the transformation of spiral arteries into utero-placental arteries is described as complete around mid-gestation. There is a gradient in the infiltration of the EVT along the spiral artery, and even in a normal pregnancy not all spiral arteries are completely transformed [18]. In humans, it is obvious that the decidua does not act

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4 as a barrier but rather as a matrix that allows the EVT cells to colonise the JZ in a
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6 regulated manner. Trophoblast invasion is notably more aggressive and more
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8 penetrative at sites of ectopic implantation, for example in the Fallopian tube, in the
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10 absence of decidua. As EVT cells differentiate, they progressively display a more
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12 migratory phenotype, changing their integrin repertoire from predominantly collagen IV
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14 receptors to fibronectin and then laminin receptors [10,15]. An array of factors operates
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16 upstream of these pathways to stimulate trophoblast invasion and includes; cytokines
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18 and growth factors, such as epidermal growth factor, vascular endothelial growth factor
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20 (VEGF), interleukin-1 β , tumour necrosis factor- α and the hyperglycosylated form of
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22 hCG; hormones, such as triiodothyronine, leptin and gonadotropin-releasing hormone-1;
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24 and low (1%) oxygen concentrations [15,18]. Equally important in the regulation of
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26 placentation are the inhibitors of trophoblast invasion. The precise regulation of
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28 trophoblast invasion will therefore depend on the balance of local concentrations of
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30 many factors, and also the composition of the extracellular matrix.
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39 We have recently reviewed the main findings from histopathologic studies in PAS
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41 [15,18], which are displayed in Table 1. There are wide variations in study design,
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43 accreta definition, number of cases studied, type of tissue investigated and the extent of
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45 quantification of morphological changes. In brief, the villous tissue shows no
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47 morphological changes in PAS compared to non-accreta placentas, even in the invasive
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49 areas (Fig. 2). The syncytiotrophoblast in PAS villous tissue shows reduced
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51 immunostaining for MicroRNA-34a, E-cadherin (E-CAD), epidermal growth factor EGF
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53 c-(erbB-2), transforming growth factor beta (TGF- β), vascular endothelial growth factor
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55 receptor 2 (VEGFR-2) and endothelial cell receptor tyrosine kinase (RTK) Tie-2. By
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4 contrast, there is increased syncytiotrophoblast labelling for epidermal growth factor
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6 receptor (EGFR) and TIMP-1 tissue inhibitors of matrix metalloproteinase (TIMP-1) in
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8 PAS. These data suggest that abnormal villous adherence develops as a result of
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10 abnormal expression of growth-, angiogenesis- and invasion-related factors in the
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12 different trophoblast populations. Lower expression of MicroRNA-34a may indicate a
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14 dysregulation of the trophoblastic cellular invasive capacity. However, the villous
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16 syncytiotrophoblast has no invasive capacity and there is no evidence that these
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18 biological changes have any impact on overall feto-placental development. Thus, these
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20 data are difficult to interpret and could be secondary to a focal environmental change in
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22 utero-placental blood flow, in particular in the oxygen concentration changes within the
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24 intervillous space in the invasive areas.
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32 EVT cells in PAS are increased in size and number, as well as in the depth of
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34 myometrial invasion. However, they form fewer MNGCs, indicating that they have not
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36 undergone their normal terminal differentiation. Immunohistochemistry has shown
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38 increased vascular endothelial growth factor (VEGF) and phosphotyrosine in EVT cells
39
40 from PAS cases compared to normal controls [16]. EVT cells lose their invasive
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42 phenotype through syncytial-type fusion into MNGCs, and the secretion of VEGF by
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44 MNGCs is likely to be one of the signals initiating and coordinating vascularization in the
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46 decidua and placenta during implantation. Lower immunostaining for soluble fms-like
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48 tyrosine kinase (sFLT-1), which is a potent antiangiogenic growth factor, has been
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50 observed in the EVT cells of women presenting with PA. These findings suggest that
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52 VEGF and sFLT-1 play pivotal roles in the process of pathological programming of
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54 EVT cells toward increased motility and invasiveness in PAS.
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4 Placenta increta and percreta are not due to a further invasion of EVT in the
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6 uterine wall. They are likely to arise secondary to the dehiscence of a scar, leading to
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8 the presence of anchoring villi deep within the uterine wall, and thus giving EVTs
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10 greater access to the deep myometrium and beyond. Overall, these results suggest that
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12 accreta placentation does not arise through excessive EVT invasiveness or proliferation
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14 and that the absence of the JZ is of more importance in the pathogenesis. The
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16 comparison of ultrasound features of uterine caesarean scar with histological findings
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18 has shown that large and deep myometrial defects are often associated with absence of
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20 re-epithelialisation of the scar area [10,15]. These findings also emphasise the role of
21
22 the sub-decidual myometrium of the JZ in modulating placentation. The absence of
23
24 decidua in first-trimester cases of PA negates previous suggestions that decidua is
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26 normal at the beginning of gestation and atrophies as pregnancy proceeds [15].
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37 ***Characteristics of utero-placental vasculature in PAS***

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39 In invasive PAS, EVTs can be found beyond the JZ and chorionic villi inside myometrial
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41 vascular spaces [15,18]. This leads to an absence of the normal plane of cleavage and
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43 prevents placental separation after delivery. Major haemorrhage occurs when the
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45 condition has not been diagnosed prenatally and manual placental delivery is
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47 attempted. Invasion of larger vessels in the outer myometrium as far as the uterine
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49 serosa in PAS is most certainly determined by access rather than a trophoblastic
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51 malfunction. Deeper than normal EVT invasion through the entire depth of the
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53 myometrium transforms the arterial vasculature beyond the JZ [18,19]. In cases of pre-
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55 existing scar defects, EVT cells can infiltrate directly the tissue around the radial and
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4 even the arcuate arteries leading to their excessive dilatation [18]. This is the most
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6 prominent feature of invasive PAS prenatally on ultrasound, and macroscopically on the
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8 uterine surface at delivery. It is possible these utero-placental vascular changes in the
9
10 accreta area result from both neovascularization and/or increased recruitment of deep
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12 uterine vessels by EVT and chorionic villi beyond the JZ.
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16 Although the numbers of interstitial EVT cells are increased in PAS, several
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18 authors have found that spiral artery remodeling is focally reduced. The deficiency is
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20 seen more in PAS cases without local decidua [15], and remodeling is sometimes
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22 completely absent in the accreta area [19]. Even the most invasive forms of PAS
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24 pregnancies are not associated with a higher incidence of placental-related disorders
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26 such pre-eclampsia and/or fetal growth restriction. These disorders are due to a
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28 reduction in trophoblast invasion and failure of conversion of the spiral arteries most of
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30 which retain their vaso-reactivity beyond 22 weeks of gestation. Pre-eclampsia is
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32 essentially a disorder affecting primigest women with ethnic variations whereas PAS is
33
34 a disorder of multiparous with no influence of ethnicity. One can hypothesize that in the
35
36 absence of a decidua, the normal release of proteases and cytokines from activated
37
38 maternal immune cells is missing, impairing arterial remodelling. This phenomenon is
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40 limited to the scar area in PAS and thus unlikely to lead to a systemic disorder such as
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42 pre-eclampsia.
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53 **ULTRASOUND-PATHOLOGIC CORRELATIONS**

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57 Ultrasound imaging and in particular colour-Doppler imaging (CDI) have enabled the
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59 investigation *in vivo* of the development of placental circulations in normal and abnormal
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1 pregnancies from the first weeks after implantation. There are now more than 1000
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4 cases reports and case series describing the prenatal diagnosis of PAS at different
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7 gestational ages, providing a unique insight into the development of accreta placental
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10 tissue and its interaction with the uterine wall. However, ultrasound studies of accreta
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13 placentation have been as heterogeneous as the histopathologic studies, in particular
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16 regarding the terminology used to describe the different ultrasound signs associated
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19 with PAS and the lack of detailed histopathologic correlations [14]. In 2016, The
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21 European Working Group on Abnormally Invasive Placenta (EW-AIP) and the Ad-hoc
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23 International AIP Expert Group [20] proposed standardized descriptions for reporting the
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26 ultrasound signs used for the prenatal diagnosis of PAS (Table 2). To facilitate the etio-
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29 pathologic analysis of the ultrasound changes associated with PAS, we have separated
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31 them according to their uterine or placental origin:
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35 ***Anomalies of the uterine wall***

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38 After a full-term pregnancy, the myometrium remains thinner and more elastic in
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41 subsequent pregnancies. If the pregnancy has resulted in a CD, the anterior portion of
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44 the lower uterine segment will be transformed by the scarring process(es) into an area
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47 where the residual myometrial tissue is mixed with fibrinous tissue. As a result, the scar
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50 area is always thinner containing less muscular tissue and thus more prone to
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53 dehiscence, in particular during the third trimester when the lower segment stretches to
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56 accommodate the growing fetus. This phenomenon will be influenced by prior multiple
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59 pregnancies and the number of prior CDs, but also by poor scarring process resulting in
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62 permanent scar defect with limited endometrial re-epithelialisation [15,18]. Not
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4 surprisingly, the ultrasound signs defined as the thinning of the uterine myometrial to
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6 <1mm and the loss of the subplacental clear zone in the myometrium under the
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8 placental bed, corresponding to the normal decidua and JZ, have been the most
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10 common findings in case reports and cohort studies [14]. In isolation, these signs are
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12 not specific of PAS (Fig. 3) and may be affected by the placental position, the pressure
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14 of the ultrasound probe, filling of the bladder and the amount of scar tissue in the
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16 myometrium.
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21 The hypervascularity of the placental bed was described more recently when CDI
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23 was used more routinely to evaluate women at high risk of PAS. In women with the
24
25 highest risk of PAS, those with prior multiple CDs and/or presenting with a low-lying or
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27 placenta praevia, hypervascularity between the myometrium and the utero-vesical
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29 posterior wall of the bladder has been reported in over 80% of cases complicated by
30
31 PAS [13,14]. CDI is not essential to confirm the diagnosis of PAS in expert hands, but
32
33 may assist in the screening of women at higher risk [13]. As uterine vascularity and
34
35 vascular dilatation increases with advancing parity, increased vascularity under the
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37 placental bed is not always pathognomonic of PAS (Fig.4 and 5).
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43 Interruption of the bladder wall with loss of the hyperechoic line between the
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45 uterine serosa and bladder lumen has been rarely described on ultrasound [14]. This
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47 sign may result from the villous invasion into the muscle of the posterior wall of the
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49 bladder in placenta percreta or may represent an ultrasound artefact arising from the
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51 massive hypervascularity of the placental bed [18]. Similarly, the presence of bridging
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53 vessels across the myometrium and beyond the uterine serosa into the bladder before
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4 disappearing has been reported inconsistently in cases of PAS [14] and may be the
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6 consequence of an ultrasound artefact [18].
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10 11 ***Anomalies of the placenta*** 12 13

14 The presence of intra-placental lacunae causing large and irregular sonolucent areas
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16 within the placental mass and giving it a “moth eaten” appearance is the most common
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18 ultrasound sign described in PAS [14]. This anomaly results from the distortion of the
19
20 normal placental cotyledonary anatomy by the unrestricted entry from the beginning of
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22 the second trimester of high velocity (turbulent) flow from the deep arterial vasculature
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24 of the myometrium [18]. Not surprisingly, in more that 50% of invasive cases of PAS
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26 feeder vessels can be seen entering the lacunae [14]. Lacunae must be differentiated
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28 on ultrasound from placental lakes (Fig. 4 and 5) which are echolucent areas in the
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30 center of a cotyledon, under the chorionic plate or in the marginal areas and are part of
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32 the normal anatomical development of the definitive placenta [18].
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38 Placental bulge distorting the extra-uterine organs and focal exophytic mass of
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40 placental tissue extending beyond the serosa have been rarely described in PAS [14]
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42 and should only been seen in cases of placenta percreta [18].
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CONCLUSIONS

The comparison of in vivo ultrasound features with histopathologic findings is essential in order to better understand the phenomenon of accreta placentation. As we can only witness the consequences of an abnormally deep EVT migration and villous attachment below the JZ at delivery, what happens during the initial phase of placentation in PAS several months previously remains a mystery. Both ultrasound features and histopathologic data support the concept that the morphological changes observed in the EVT in PAS are environmental, and the consequence of an unusual and prolonged interaction with the highly vascularised deep myometrium which these cells would normally not reach in normal placentation. Overall these findings support the concept of a primary deciduo-myometrium defect in PAS, exposing the uterine myometrium below the JZ to the migrating EVT. The loss of the normal plane of placental cleavage from the uterine wall and the excessive vascular remodelling of the radial and arcuate arteries can explain the prenatal ultrasound findings and the clinical consequence of accreta placentation, in particular in its invasive forms. Neovascularisation or dilation of the myometrial vasculature induced by the trophoblast increases the risk of haemorrhage when manual removal of an undiagnosed placenta accreta is attempted.

TEACHING POINTS

- The recent increase in placenta accreta spectrum disorders is directly linked to the increase incidence in uterine scar from previous surgery, mainly caesarean section.

- There is mounting evidence that abnormal villous adherence and/or invasion of the uterine wall is due to a defect of the junctional zone between the superficial myometrium and the endometrium.
- Macroscopic and microscopic examinations of hysterectomy specimens or myometrial samples from an abnormal placentation site remain the gold standard of reference to confirm the diagnosis of PAS.
- Trophoblast biological changes observed with immunohistochemistry in PAS are mainly secondary to the development in a different environment with no interaction with decidual tissue.
- Correlations of the ultrasound imaging from early in pregnancy with histopathological examination at birth are pivotal to better understand the natural evolution of PAS, and are essential to improve the diagnosis and management of this increasingly common major obstetric complication.
- Standardized ultrasound and clinical terminology is essential to allow direct correlations between antenatal and delivery findings in PAS and provide more accurate population epidemiology data.

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Table 1: Histopathological and immunostaining changes observed in PAS [15] according to anatomical level.

VILLOUS TROPHOBLAST

- Lower syncytiotrophoblast immunostaining for MicroRNA-34a, TGF- β , E-CAD, EGF c-(erbB-2), VEGFR-2 and RTK Tie-2.
- Higher syncytiotrophoblast immunostaining for EGFR and TIMP-1.

EXTRAVILLOUS TROPHOBLAST (EVT)

- Increased in the size, numbers and depth of myometrial invasion of EVTs
- Reduced formation of MNGCs.
- Higher EVT immunostaining for VEGF and phosphotyrosine.
- Lower EVT immunostaining for sFLT-1.

UTERO-PLACENTAL VASCULATURE

- Decreased proportion of remodelled spiral arteries.
 - Greater degree of remodelling in radial/arcuate arteries in increta and percreta.
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E-CAD= E-cadherin; EGFR= epidermal growth factor receptor; MNGCs= multinucleated trophoblast giant cells; RTK= receptor tyrosine kinase; RTPCR= reverse transcription polymerase chain reaction; sFLT-1= Soluble fms-like tyrosine kinase; TGF- β = Transforming growth factor beta; TIMP-1 tissue inhibitors of matrix metalloproteinase; VEGF= Vascular endothelial growth factor; VEGFR= Vascular endothelial growth factor receptor.

Table 2. Ultrasound signs according to gray-scale versus colour-Doppler imaging using the standardized descriptions proposed recently by the European Working Group on Abnormally Invasive Placenta (EW-AIP) and the AIP international expert group, modified from [20].

Grey-scale imaging

- Thinning of the uterine myometrium.
- Bladder wall interruption between the uterine serosa and bladder lumen.
- Loss of the subplacental clear zone.
- Intra-placental lacunae.
- Extra-uterine placental bulge.
- Focal placental exophytic mass.

Colour-Doppler imaging (CDI)

- Utero-vesical hypervascularity.
- Hypervascularity of the placental bed.
- Bridging vessels beyond the uterine serosa.
- Lacunae feeder vessels.

Figure legends

Fig 1. A. Transvaginal ultrasound view of the uterus in a non-pregnant woman with a history of 2 prior CDs. Note the scar defects through the uterine wall at the junction between the cervix and lower uterine (U) segment (arrow). **B.** Transvaginal ultrasound view of pregnant uterus at 7 weeks gestation after 3 prior CDs showing the lower end of the placenta (arrow) protruding inside a large caesarean scar defect (CSD). The pregnancy was uncomplicated delivered at 36 weeks with the edge of the placenta visible under the uterine serosa but with no clinical evidence of placenta percreta.

Fig 2. Microscopic view of the placental bed from a hysterectomy specimen at 34 weeks in a pregnancy complicated by placenta previa increta (H&E x 5) showing the disruption of the decidua by placental villi (arrow) invading the myometrium.

Fig 3. Transvaginal ultrasound view of the lower segment of the uterus in a non-pregnant woman with a history of 3 prior CDs presenting with a major placenta (P) previa covering partially the cervix. Note the uterine myometrial of <1mm in thickness and the loss of the subplacental clear zone between the placental bed and the bladder (B) wall (arrow). There was no evidence of PAS at birth.

Fig 4. Transabdominal ultrasound longitudinal views of the placental bed at 22 weeks in a pregnancy after 1 prior CD presenting with a major placenta (P) previa covering the cervix showing: **A.** areas of absent myometrium and irregular subplacental clear zone and numerous lacunae giving the placenta a “moth eaten” appearance on grey-scale imaging; **B.** increased and anarchic hypervascularity of the placental bed on CDI. An extended zone of placenta increta was confirmed at birth. F= fetus.

Fig 5. Transabdominal ultrasound longitudinal views of the placental bed at 28 weeks in a pregnancy after 2 prior CDs presenting with a major placenta (P) previa covering partially the cervix showing: **A.** area suggesting a disruption of the uterine wall between the placental bed and the bladder (B) with absent myometrium (arrow) and intraplacental lakes on grey-scale imaging. **B.** CDI indicates a normal utero-placental circulation. No PAS was found at birth. F= fetus.















